

## African Burkitt Lymphoma: Age-Specific Risk and Correlations with Malaria Biomarkers

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**Abstract.** African Burkitt lymphoma is an aggressive B-cell, non-Hodgkin lymphoma linked to *Plasmodium falciparum* malaria. Malaria biomarkers related to onset of African Burkitt lymphoma are unknown. We correlated age-specific patterns of 2,602 cases of African Burkitt lymphoma (60% male, mean  $\pm$  SD age = 7.1  $\pm$  2.9 years) from Uganda, Ghana, and Tanzania with malaria biomarkers published from these countries. Age-specific patterns of this disease and mean multiplicity of *P. falciparum* malaria parasites, defined as the average number of distinct genotypes per positive blood sample based on the merozoite surface protein-2 assessed by polymerase chain reaction, were correlated and both peaked between 5 and 9 years. This pattern, which was strong and consistent across regions, contrasted parasite prevalence, which peaked at 2 years and decreased slightly, and geometric mean parasite density, which peaked between 2 and 3 years and decreased sharply. Our findings suggest that concurrent infection with multiple malaria genotypes may be related to onset of African Burkitt lymphoma.

### INTRODUCTION

Burkitt lymphoma (BL) is an aggressive, monoclonal B-cell, non-Hodgkin lymphoma that was first described in African children in 1958.<sup>1</sup> Today, it is known to occur as three clinical-epidemiologic variants: African (aBL), sporadic (sBL), and acquired immunodeficiency syndrome (AIDS)-related BL.<sup>2</sup> Epstein-Barr virus (EBV), discovered in aBL tumors in 1964<sup>3</sup> and subsequently shown to be ubiquitous,<sup>4</sup> is linked to aBL and several other malignant and non-malignant conditions.<sup>5</sup> EBV is detected as clonal episomal or integrated DNA or as RNA in 95% of aBL tumors.<sup>6</sup> In areas with a high incidence of BL, almost all children are infected with EBV by 2–3 years of age,<sup>7</sup> well before peak age at aBL onset. This suggests that increased risk for aBL may be influenced by chronic, not acute, EBV infection.<sup>6</sup> EBV infection is demonstrable up to 60 months before the onset of aBL.<sup>6</sup> However, EBV is not essential for aBL because most persons who are infected do not develop aBL, and it appears to play a less prominent role in sBL and AIDS-related BL because it is detected in at most 10–20% and 30–40% of cases, respectively.<sup>8</sup>

African BL occurs in the context of *Plasmodium falciparum* malaria, which is presumed to be geographical co-factor of aBL,<sup>9,10</sup> based on parallel distribution of both diseases.<sup>10,11</sup> The carriage of the sickle cell gene, a genetic marker for reduced risk of severe malaria, was significantly or marginally reduced in children with aBL<sup>12</sup> compared with hospital-based controls without aBL in two studies,<sup>13,14</sup> but not in the third study.<sup>15</sup> These findings, based on studies conducted more than 40 years ago, provide some support for an etiologic role of malaria in aBL. Two case-control studies recently conducted in Uganda and Malawi demonstrated 5-fold and 12-fold odds ratio, respectively, of elevated antibodies against malaria among children with aBL compared with controls.<sup>16,17</sup>

*Plasmodium falciparum* malaria induces polyclonal expansion of B-cells, impairs EBV-specific T cell immune responses,<sup>18</sup> and may preferentially stimulate the expansion of EBV-positive B cells expression by its cysteine-rich interdomain region 1 $\alpha$ , a *P. falciparum* erythrocyte membrane protein 1 receptor,<sup>19</sup> all of which suggest a biological basis for how malaria may influence the risk for aBL. The biomarkers of malaria infection e.g., parasite prevalence, density, or genotypes, that may be related to onset of aBL are unknown. We performed an ecologic correlation of the age-specific incidence in a historical aBL case-series from Uganda, Ghana, and Tanzania with various malaria biomarkers published in studies conducted in countries where cases were detected to generate hypotheses about malaria biomarkers that may be related to onset of aBL.

### MATERIALS AND METHODS

**Cases of aBL.** The cases (in persons 0–14 years of age) were from four large studies conducted in Uganda,<sup>20,21</sup> Ghana,<sup>22</sup> and Tanzania<sup>23</sup> during 1964–2009. The data from Uganda came from two studies, one conducted in the southern region, where the incidence of aBL is low,<sup>11</sup> and the other in the northern region, where the incidence is high.<sup>11,20</sup> Data from southern Uganda was obtained from the Kampala Cancer Registry (KCR) for cases registered during 1990–2009. The KCR is a population-based registry that covers approximately 1.8 million persons in Kampala, the capital city, and its immediate environs.<sup>24</sup> Cancer registrars actively search records at local hospitals to find new cases. Coverage for KCR was estimated to be approximately 90% complete for cases diagnosed during 1994–1996.<sup>25</sup> Data from northern Uganda were obtained from St. Mary's Hospital in Lacor for cases from 10 districts in northern Uganda and they were diagnosed and treated at the hospital during 1997–2006.<sup>20</sup> Because there were no other hospitals with capacity to diagnose and treat aBL in the region, these data were assumed to be almost complete for cases arising in the 10 neighboring districts served by the hospital (approximately a 100-mile radius). Data from Ghana were obtained from the National Cancer Institute (USA)

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Burkitt’s Tumor Project for cases in persons who originated mostly from the southern half of Ghana and were enrolled at Korle Bu Hospital, Accra, during 1965–1989.<sup>22</sup> Data from Tanzania were obtained from Shirati Hospital for cases in persons from the North Mara region who were diagnosed and treated during 1960–2009.<sup>23</sup> Completeness of these series is uncertain, but they were thought to be representative of the cases from the regions served by the hospitals.

**Malaria genotypes and other biomarkers.** We compiled data on *P. falciparum* malaria biomarkers from published literature of studies conducted in the countries where the cases arose identified from PUBMED. These biomarkers included parasitemia prevalence (percentage of persons with a positive blood slide for parasites among all persons tested), geometric mean parasite density (GMPD), and multiplicity of infection (MOI), defined as the average number of distinct genotypes, based on the merozoite surface protein-2 (MSP-2) per positive blood sample tested by polymerase chain reaction.<sup>26–28</sup> The MSP-2 genotypes were based on two allelic variants (IC = 400–750 basepairs and F27 = 250–500 basepairs), which were determined by using polymerase chain reaction primers specific for highly conserved regions flanking polymorphic domains of the gene block 3 of the MSP-2 gene.<sup>26–28</sup> Monthly rainfall data for the study regions, Gulu and Kampala, Uganda (2004–2008),<sup>29</sup> Accra, Ghana (1952–1970),<sup>30</sup> and Shirati Hospital, Tanzania (1980–2008 from local measurements provided by co-author), were correlated with monthly percentage of aBL cases lagged by 1–4 months by using Pearson’s correlation coefficient to explore correlation between monthly rainfall and monthly aBL case incidence.

Descriptive analysis were performed by using frequency tables for categorical variables: sex, anatomic tumor site (face or head tumors only; abdominal for tumors involving abdominal visceral organs with or without face or head involvement;

and other or unspecified anatomic sites, including the central nervous system), age group (0–14 years in 3-year intervals), and calendar-year period (1960–2009 in 10-year intervals) in SAS version 9.1 (SAS Institute, Cary, NC). Chi-square tests and Student’s *t*-test were performed to assess associations between categorical and continuous variables, respectively, with aBL. Pearson’s correlation coefficients were calculated to assess strength of association between age-specific patterns of aBL cases with malaria biomarkers. Age-specific patterns of aBL and of malaria biomarkers were graphed by using R under the terms of the Free Software Foundation GNU General Public License (version 2.11.1, May 2010, The R Foundation for Statistical Computing). *P* values < 0.05 were considered statistically significant.

RESULTS

Based on 2,602 aBL cases included in the study, the male:female case ratio was 1.5:1 for cases in the four regions combined, ranging from 1.2:1 in southern Uganda to 1.8:1 in northern Uganda (Table 1). The mean ± SD age for cases in all regions was 7.1 ± 2.9 years and it was non-significantly lower in boys than girls (6.9 years versus 7.3 years; *P* = 0.07). By region, mean age at diagnosis was lowest in cases from northern Uganda and the highest in cases from Ghana (6.6 years versus 8.0 years; *P* = 0.09). Only 2.4% of cases were 0–2 years of age; most (69.1%) were 3–8 years of age and 28.4% were 9–14 years of age. Anatomic tumor site information that was complete for 69% of cases, of whom most (61.1%) had abdominal involvement, with or without involvement of face or head, and 33.0% had face or head involvement only. Compared with boys, girls appeared to have more abdominal involvement, but the result was not significant (68.6% versus 56.1%; *P* = 0.25). Children with tumors involving the face or head were younger than children

TABLE 1  
Characteristics of African Burkitt lymphoma cases in persons 0–14 years of age, by country

Characteristic	All countries		Uganda (southern)		Uganda (northern)		Ghana		Tanzania	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
All persons	2,602		371		500		581		1,150	
Sex*										
Male	1,551	59.7	206	55.5	324	64.8	363	62.5	658	57.5
Female	1,046	40.3	165	44.5	176	35.2	218	37.5	487	42.5
Unknown	5		0		0		0		5	
Tumor site*										
Face or Head	594	33.0	0	0.0	177	37.9	173	29.8	244	32.5
Abdominal	1,099	61.1	0	0.0	280	60.0	321	55.2	498	66.4
Other	105	5.9	0	0.0	10	2.1	87	15.0	8	1.1
Unknown	804		371		33		0		400	
Age group, years*										
0–2	63	2.4	13	3.5	8	1.6	6	1.0	36	3.2
3–5	791	30.6	118	32.0	206	41.2	110	18.9	357	31.4
6–8	998	38.6	133	36.1	179	35.8	238	41.0	448	39.5
9–11	464	18.0	68	18.4	66	13.2	140	24.1	190	16.7
12–14	269	10.4	37	10.0	41	8.2	87	15.0	104	9.2
Unknown	17		2		0		0		15	
Mean (SD)	7.1 (2.9)		6.9 (3.0)		6.6 (2.6)		8.0 (2.8)		6.9 (2.8)	
Diagnosis year*										
1960–1969	117	4.6	0	0.0	0	0.0	60	11.0	57	5.0
1970–1979	392	15.3	0	0.0	0	0.0	283	51.7	109	9.4
1980–1989	371	14.4	0	0.0	0	0.0	203	37.1	168	14.6
1990–1999	673	26.2	159	42.9	75	15.0	1	0.2	438	38.1
2000–2009	1,015	39.5	212	57.1	425	85.0	0	0.0	378	32.9
Unknown	34		0		0		34		0	

\* Percentage excludes unknown category.

with tumors involving abdominal and/or other or unspecified sites (mean age = 6.4 years versus 7.5 years;  $P = 0.02$ ).

The percentage of aBL cases peaked near five years and then decreased gradually thereafter. The pattern for mean MOI of *P. falciparum* resembled the age-specific pattern for aBL, including increasing gradually with age to a peak near five years and then decreasing gradually (Figure 1A and B for Ghana and Tanzania; not shown for Uganda). Strong correlations were demonstrated between age-specific patterns for aBL and MOI in all regions: southern Uganda (Pearson's correlation coefficient 0.91,  $P = 0.01$ ), northern Uganda (Pearson's correlation coefficient 0.89,  $P = 0.02$ ), Ghana (Pearson's correlation coefficient 0.90,  $P = 0.002$ ), and Tanzania (Pearson's correlation coefficient 0.77,  $P = 0.01$ ). This pattern contrasted that of prevalence of *P. falciparum* malaria parasitaemia and GMPD, which increased rapidly and peaked by two years of age and decreased only slightly thereafter for parasitaemia, but decreased rapidly to levels much below the peak by four years of age for GMPD (Figure 1C and D for Ghana and Tanzania; not shown for Uganda).

Monthly aBL cases lagged by four months were unrelated with monthly rainfall in all regions (northern Uganda: Pearson's correlation coefficient = 0.48,  $P = 0.12$ ; Ghana: Pearson's correlation coefficient = -0.15,  $P = 0.65$ ; Tanzania: Pearson's correlation coefficient = 0.10,  $P = 0.79$ , except in southern Uganda where the correlation was marginal (Pearson's correlation coefficient = 0.57,  $P = 0.05$ ).

## DISCUSSION

The novel finding of our study is the strong and consistent correlation of age-specific patterns of aBL with age-specific

patterns of concurrent malaria genotypes of *P. falciparum* malaria. This pattern contrasted sharply from that of asymptomatic parasitaemia prevalence and GMPD peaked approximately two years before the peak age for aBL and either remained elevated, as for parasitaemia, or decreased rapidly, as for GMPD. Although ecologic, our findings support the hypothesis that genetic complexity of *P. falciparum* malaria infections and the associated immune response they trigger may be related to the onset of aBL. The prevalence and pattern of MOI with age is likely a function of the joint probability of exposure to diverse strains of *P. falciparum* malaria circulating in a given population and probability of developing cumulative immunity against any given strains circulating in the community.<sup>31</sup> MOI is associated with elevated risk for clinical malaria among non-immune persons<sup>32</sup>. Conversely, it is associated with decreased risk from clinical malaria among persons with developed anti-malarial immunity,<sup>33</sup> but its relationship with aBL has not hitherto been examined. MOI may be a surrogate for immunologic consequences of exposure to mixed genotype malaria infections and the greater propensity for aBL to be triggered in such persons.<sup>34</sup>

Few aBL cases were noted among children 0–2 years of age. This paucity sharply contrasts with the burden of malaria, which is typically high in this age group. The paucity of aBL cases in this age group argues against prenatal initiation of aBL accelerated by early childhood infections in the etiology of aBL. The sparseness of cases may be caused by competing mortality from acute severe malaria syndromes or to under-ascertainment of cases in infants and toddlers. Under-ascertainment is unlikely to account for major deficits because aBL in young children frequently involves the face or head anatomic sites and tumors at these sites are easily recognized

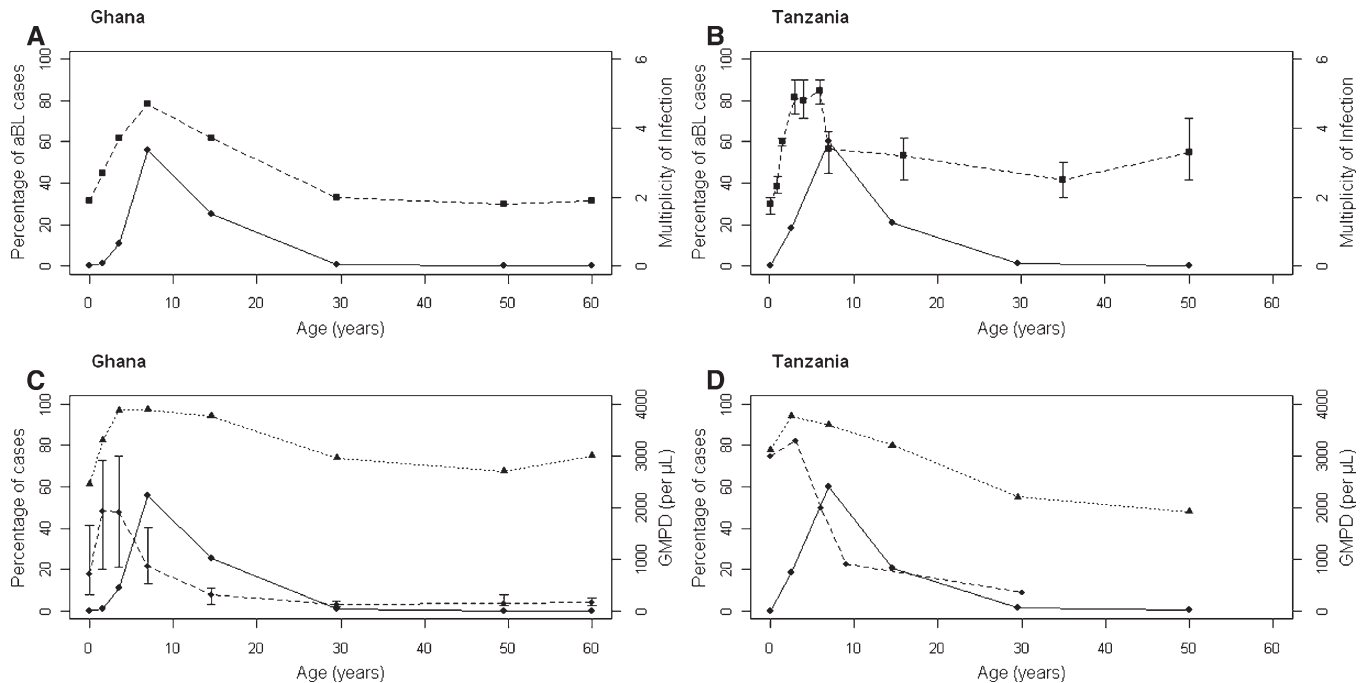


FIGURE 1. Characteristics of African Burkitt lymphoma cases correlated with *Plasmodium falciparum* malaria mean multiplicity of infection, prevalence, and geometric mean parasite density. **A** and **B**, Percentage of African Burkitt lymphoma cases by age and mean multiplicity of *P. falciparum* malaria parasites, defined as the average number of distinct genotypes per positive blood sample based on the merozoite surface protein-2 assessed by polymerase chain reaction, in Ghana<sup>27</sup> and Tanzania.<sup>26</sup> **C** and **D**, Percentage of African Burkitt lymphoma cases per age, prevalence of *P. falciparum* malaria, and geometric mean parasite density in the general population in Ghana<sup>27</sup> and Tanzania.<sup>26,39</sup> Age group intervals for the cases were plotted according to the age groups used in the malaria papers.

by the parents, and would be recognized as aBL by clinicians practicing in regions where aBL is endemic.

We found that the age at onset for aBL in Ghana was higher than that in northern Uganda. The regional disparities in mean age at aBL may be caused by differences in the intensity of malaria in these countries, differences in the specific malaria genotypes circulating in the countries, or to other factors correlated with malaria, such as helminthic parasites, which may be different between Ghana and northern Uganda. We found that males predominate in all regions and are more likely to be diagnosed with aBL at a young age and to have tumors that involve the face or head in cases from all regions. Male predominance is also observed in sBL and AIDS-related BL,<sup>35</sup> suggesting that males may be genetically predisposed to BL independent of geographic origin of the cases and of antecedent illnesses, including EBV, malaria, or human immunodeficiency virus. Monthly rainfall was not correlated with aBL incidence, in accordance with some studies,<sup>36,37</sup> but not all studies.<sup>38</sup> The poor correlations between rainfall and aBL, although rainfall is associated with increase in malaria transmission, may be caused by a negative impact of heavy rainfall on medical-seeking behaviors of persons in rural areas or an influence of other factors modulated by rainfall, such as co-transmission of soil transmitted parasites and/or viral infections or nutrition, whose effects may distort and obscure correlations of rainfall with aBL incidence.

Our study has limitations. Our findings are based on an ecologic analysis using historical hospital-based case-series over many years and markers compiled from published malaria data. Both data sets are of uncertain accuracy in their case diagnosis and completeness. The cases and malaria data compiled were sometimes from different time periods and different areas, which should be considered when interpreting the correlations. Because our results for MOI are based only on one gene, our conclusions about genetic diversity of malaria and aBL must be interpreted cautiously. The malaria results are subject to publication and other biases, but such systematic bias would probably attenuate the patterns, correlations, and the consistency in diverse areas studied. The strengths of our study include its large numbers, wide geographic area covered, which gives some reassurance about generalizability of the patterns we demonstrated, and novelty of assessing age-specific patterns to develop clues about etiology.

In conclusion, we demonstrated the expected patterns of male predominance, the young age of onset of aBL, especially on the face and head among boys, and later age onset, especially for tumors in the abdomen among girls using historical data of aBL case series from Uganda, Ghana, and Tanzania. The novel findings were the strong and consistent correlations between age-specific patterns of aBL with those for MOI of *P. falciparum* malaria, which have not been previously shown. Our results support the hypotheses that mixed genotypic infections and, perhaps associated immunologic immune responses, may be related to onset of aBL.

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